Volume 98 Number 4
April 1991
ISSN 0161-6420

Ophthalmology

The Journal of the
American Academy of Ophthalmology

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Published by
J. B. Lippincott Company

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American Academy of Ophthalmology

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Second class postage paid at Hagerstown, MD, and at additional mailing offices.

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POSTMASTER: Send address changes to Ophthalmology, Downsville Pike, Route 3, Box 20-B, Hagerstown, MD 21740.

Use of Bioerodible Polymers Impregnated with Mitomycin in Glaucoma Filtration Surgery in Rabbits

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Abstract: A prospective, randomized, double-masked, and placebo-controlled study was performed to evaluate the effects of a localized and sustained release of mitomycin on the success of glaucoma filtration surgery in rabbits. A bioerodible polymer was used as the drug carrier. Full-thickness filtration surgeries were performed and data from 22 rabbits were collected. One eye received a polymer impregnated with mitomycin (0.02 mg or 0.06 mg), while the fellow eye received a drug-free polymer. Intraocular pressure, bleb survival, and postoperative complications were investigated. Intraocular pressures remained lower for a longer period of time ($P < 0.004$) and filtration blebs lasted longer ($P < 0.05$) in experimental eyes than in control eyes. Conjunctivitis and sectoral corneal haze occurred more frequently in eyes treated with the higher dosage mitomycin compared with control eyes. The use of mitomycin-C in a polymer delivery system appeared to promote the success of glaucoma filtration surgery in rabbits. With the lower dosage of mitomycin, clinically significant ocular toxicity was not noted. *Ophthalmology 1991; 98:503–508*

Fibroblast proliferation and migration have been implicated in glaucoma filtration surgery wound healing.[1-2] Various antifibroblastic agents, therefore, have been used experimentally to delay this healing process. The antimetabolite 5-fluorouracil, injected subconjunctivally, is, at present, the agent of choice for adjunctive treatment to filtration surgery in eyes of patients with glaucoma who have poor surgical prognoses.[3-5] Mitomycin, an alkylating agent isolated from *Streptomyces caespitosus*, has been used topically to improve the success rate of full-thickness filtration surgery in rabbits[6] and trabeculectomies in humans.[7,8] Although few serious side effects have been reported with the ocular use of these agents,[9-12] the need for frequent administration and ocular surface toxicity are significant drawbacks to their use. These disadvantages may be eliminated by adopting different drug delivery systems, which provide a localized and sustained release of drug.[13-17] We examined the effect of mitomycin-impregnated bioerodible polymer discs on glaucoma filtration surgery in rabbits.

Originally received: August 6, 1990.
Revision accepted: December 14, 1990.

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Presented at the Association for Research in Vision and Ophthalmology Meeting, Sarasota, April 1990.

Supported by NIH grants EY07701 and EY00331 and the Lucille Ellis Simon Glaucoma Research Fund.

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MATERIALS AND METHODS

The following chemicals were obtained: mitomycin-C (Bristol Meyers Company; Syracuse, NY), ketamine

(Parke-Davis; Morris Plains, NJ), xylazine (Haver-Lockhart; Shawnee, KS), and pentobarbital (Abbott Laboratories; North Chicago, IL).

The copolyanhydride of bis (p-carboxyphenoxy) propane and sebacic acid, in a ratio of 25:75 by weight, was used as the carrier matrix. The polymers were synthesized by a melt–condensation technique.[17] The chemical structure of the polymer was confirmed by Fourier transform infrared spectroscopy. Gel permeation chromatography was used to characterize the molecular weight distribution of the polymer; an average molecular weight of 42,000 was found.

The mitomycin-impregnated implants, 3 mm in diameter and 1 mm thick, were fabricated by compression molding in two stages at room temperature. To eliminate the burst effects in the drug release kinetics, a laminate design was used. In the first molding, 1 mg of drug was mixed with 7 mg of polymer and compressed at an approximate pressure of 5 Kpsi for 5 minutes. The sample was then placed in the mold for a second compression, with 1 mg of polymer on each side of the disc, at an approximate pressure of 13 Kpsi for 15 minutes. The control implants were made in the absence of drugs with only one compression (13 Kpsi and room temperature for 10 minutes). All implants were stored dessicated in a bottle. The first 12 implants contained 0.02 mg of mitomycin and the last 14 contained 0.06 mg of mitomycin. Drug release experiments were conducted in a 0.1 M pH 7.4 phosphate buffer containing 0.02 weight/percent of sodium cacodylate or gentamicin sulfate to inhibit bacterial growth. The drug-loaded matrices were placed in 10 ml of buffer in 20 ml vials and incubated at 37° C. The buffer solutions were changed five times during the first day and twice daily afterward to approximate perfect sink conditions and to ensure that the drug concentration remained below its saturation value. Solutions were then subject to high-pressure liquid chromatography analysis.

The study design was prospective, randomized, double-blind, and placebo-controlled. Normal pigmented rabbits, each weighing between 2 and 4 kg, underwent preoperative eye examination with a Zeiss slit-lamp biomicroscope. Preoperative intraocular pressure (IOP) was measured by pneumotonometry after the instillation of one drop of 0.5% proparacaine hydrochloride to each eye (Alcon Applanation Pneumotonograph, Digilab Inc, Cambridge, MA). The average of three measurements was used as the preoperative IOP. Criteria for termination were the return of IOP to within 2 mmHg from baseline preoperative IOP, completion of an 8-week postoperative course, death, or ocular infection. Exclusion criteria were intraoperative complications of conjunctival buttonhole and vitreous at the sclerostomy site. This study conformed to the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Research and was approved by the Division of Ophthalmology of the King/Drew Medical Center, the Department of Ophthalmology of the University of California at Los Angeles, and the Department of Biomedical Engineering of the Johns Hopkins University.

General anesthesia was induced with ketamine 50 mg/kg intramuscularly and xylazine 15 mg/kg intramuscularly. Surgery was performed by the same surgeon on both eyes of each rabbit. A lid speculum was inserted to expose the globe. The conjunctiva was incised superotemporally near the fornix with Wescott scissors. Tenectomy was then performed to expose the underlying sclera, followed by careful conjunctival dissection anteriorly to the limbus. A 5-mm limbal groove that extended 3 mm into clear cornea was made with a 57 Beaver blade. A paracentesis was made into clear peripheral cornea nasally. The anterior chamber was then entered at the filtration site with a 15° blade. A 1-mm × 3-mm sclerostomy was made with the Kelly-Descemet punch followed by cautery of the posterior lip. A peripheral iridectomy was then performed with Vannas scissors and curved jeweler's forceps. One eye of each rabbit was randomized to determine which one would receive mitomycin-impregnated polymer versus the control drug-free polymer. The polymer was then positioned adjacent to the sclerostomy. The conjunctiva was repositioned over the polymer and the wound closed with 10-0 nylon suture in a continuous fashion. Sterile saline was injected through the paracentesis to reform the anterior chamber. After ensuring that the wound was water-tight, topical Sulf 10 ophthalmic ointment was instilled. Additional antibiotics or steroids were not used in the postoperative period.

Postoperatively, rabbit eyes were examined by an observer who was masked with respect to randomization status. Rabbits were examined every other day initially and then every third day for a total of 8 weeks. Slit-lamp biomicroscopy and IOP measurements by pneumotonometry were performed during each examination. Polymer duration and the appearance of the bleb, conjunctiva, cornea, anterior chamber, and lens were noted. At study termination, animals were sacrificed with an overdose of sodium pentobarbital, 75 mg/kg intravenously and the eyes were harvested for histologic examination. All eyes were stored in 10% neutral buffered formalin.

Before surgery, four rabbits were designated to be sacrificed at 14 days postoperatively. The data from the eyes of these rabbits were not used in the statistical analysis. Rather, these eyes were used solely for pathologic study during a pretermination stage. After enucleation, three pairs of eyes were immediately immersed in 10% neutral buffered formalin while the fourth pair was immersed in gluteraldehyde 2%. Eyes from rabbits completing the study as well as from those specifically sacrificed during the designated pretermination stage were later sectioned for pathologic examination. The eyes were sectioned near the sclerostomy sites and examined by gross and microscopic methods as previously described for human eyes.[18] They were examined by a pathologist (BJG) who was not aware of the treatment status of the eyes.

Surgery was performed on 28 rabbits. As mentioned previously, before randomization, four rabbits were designated to be sacrificed at 2 weeks postoperatively for pathologic examination. Two additional rabbits sustained intraoperative complications and were excluded from the study before treatment randomization: one suffered vitreous loss and hyphema and the other sustained a large

conjunctival buttonhole. Therefore, data were collected from 22 rabbits (44 eyes). Of these rabbits, 12 received 0.02 mg of mitomycin, and the last 10 rabbits received 0.06 mg. Separate statistical analyses of these two groups of rabbits were performed with respect to the change of IOP from baseline preoperative IOP, the time to bleb failure, conjunctival injection, and anterior chamber inflammation. Similar trends were noted between groups in these analyses. Therefore, the two groups of rabbits were combined, and the results of both the separate and combined analyses are presented.

Statistical analysis was performed to compare the experimental eye of each rabbit with the fellow control eye. Variables analyzed included IOP, time to IOP failure, time to bleb failure, conjunctival injection, anterior chamber inflammation, corneal clouding, and cataract formation. Comparison of variables were performed using the paired *t* test, repeated measures analysis of variance, sign rank test, and the life-table analysis using McNemar's statistic for paired data[19] as appropriate.

Repeated measures analysis of variance was used to compare the pairs of treated and control eyes using the differences from the baseline IOP for each eye. Change in IOP from baseline directly addresses the study hypothesis and takes into account differences between paired eyes with respect to preoperative IOP levels. The comparison of treatment eyes to fellow control eyes with respect to change from baseline IOP is statistically superior, more informative, and has greater precision than the mere comparison of postoperative IOPs. Only rabbits followed for the entire study period (at least 53 days) were included in the repeated measures analysis. This analysis allowed investigation into the question of whether the pairs of eyes differed over the overall study period. A paired *t* test at each day was used to delineate the portion of the overall study period where the pairs of eyes were significantly different from one another. Survival analysis, using the product-limit method, was used to take into account the data from censored observations and to demonstrate the temporal sequence of filtration surgery failure as defined by postoperative IOP status and bleb morphology. Differences between groups with respect to time of failure were assessed using the paired sign test of Seigel and Podgor.[20] A level of $P < 0.05$ was considered to be statistically significant for all analyses.

RESULTS

Mitomycin as received commercially is mixed with 24 parts of sodium chloride for higher aqueous solubility. The release rate of that mixture from the carrier was high due to the high driving force for diffusion. Initial release studies indicated that 100% of the drug was released within the first 24 hours. To obtain a more sustained release, a laminar design in which the pellets were coated by a thin film of the same polymer was used. In that case, the drug was almost completely released in 48 hours. To further reduce the rate of drug release, the sodium chloride was removed from the mixture. The in vitro release kinetics of the net mitomycin is shown in Figure 1. The profile is characteristic of a release mechanism controlled by both drug diffusion and matrix degradation. It must be pointed out that the subconjunctival space might not act as a perfect sink for the removal of the drug, as simulated in the in vitro studies. Hence, the driving force for the drug release might be lower, which would lead to a more sustained release in vivo.

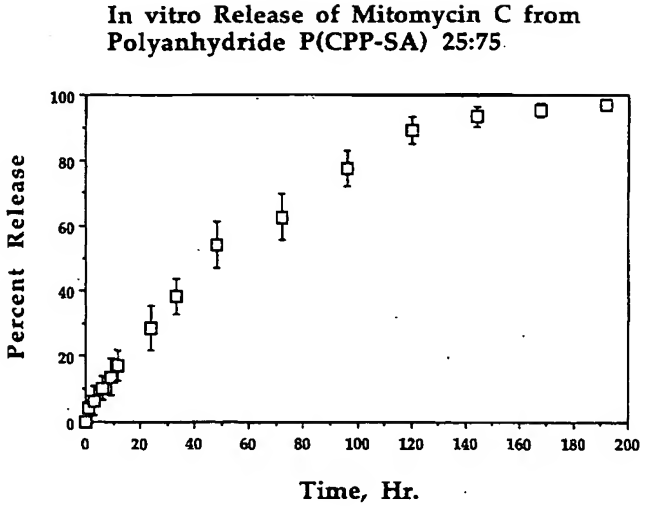

Fig 1. In vitro polymer degradation and release of mitomycin-c over time in hours. PCPP-SA 25:75 denotes bis (p-carboxyphenoxy) propane and sebacic acid in a ratio of 25:75 by weight.

Of the 44 randomized eyes, 35 failed by IOP criterion, 5 eyes reached study termination due to development of conjunctivitis, and 4 eyes were lost due to the unexpected death of two rabbits. Mean preoperative IOP, immediate postoperative IOP, and polymer durations for all 44 eyes are presented in Table 1. No differences were noted between the control group and the two experimental groups in any of these parameters.

In the overall group of 22 rabbits, the mean preoperative IOP for the 44 eyes was 21.1. mmHg ± 5.0 mmHg for mitomycin-treated eyes and 21.2 mmHg ± 4.5 mmHg for control eyes. The mean postoperative IOP measured 2 days after surgery was 13.1 mmHg ± 6.2 mmHg for experimental eyes and 11.5 mmHg ± 6.6 mmHg for control eyes. Repeated measures analysis was used to assess differences in postoperative IOP reduction between experimental and control eyes for the 15 rabbits who completed the entire study without ocular or systemic complications. In the group in which 0.02 mg of mitomycin was used, postoperative IOP reduction over the course of the study was greater for experimental eyes compared with control eyes. The difference between eyes was statistically significant from postoperative days 6 to 22 ($P < 0.05$). Eyes treated with 0.06 mg of mitomycin also had greater IOP reduction compared with control eyes over the course of the study with statistically significant differences noted from days 8 to 18 ($P < 0.05$). When data from both groups were combined, the postoperative reduction in IOP was

Table 1. Early Intraocular Pressure Response and Polymer Duration for Mitomycin and Control Eyes

	Mitomycin Eyes	Control Eyes	P*
0.02 mg mitomycin (n = 12)†			
Baseline IOP (mmHg)‡	22.0 ± 3.9	22.0 ± 4.1	1.00
First postoperative IOP	25.3 ± 7.3	13.8 ± 8.1	0.32
Polymer duration (days)	7.2 ± 2.3	7.3 ± 2.8	0.78
0.06 mg mitomycin (n = 10)			
Baseline IOP (mmHg)	20.1 ± 6.2	20.2 ± 5.1	0.89
First postoperative IOP	10.5 ± 3.1	8.8 ± 2.2	0.20
Polymer duration (days)	9.4 ± 2.5	9.6 ± 2.4	0.34
Dose levels combined (n = 22)			
Baseline IOP (mmHg)	21.1 ± 5.0	21.2 ± 4.5	0.92
First postoperative IOP	13.1 ± 6.2	11.5 ± 6.6	0.10
Polymer duration (days)	8.2 ± 2.6	8.4 ± 2.4	0.58

* Results of paired *t* test of hypothesis that treatment and control eyes are equal.
† Number of rabbits.
‡ Preoperative intraocular pressure.

significantly greater for treated eyes compared with control eyes for postoperative days 8 through 25 ($P < 0.004$) (Fig 2).

Survival analysis was used to assess information from all 44 randomized eyes inclusive of eyes for which data were censored secondary to ocular complications or death. With IOP failure defined as return of postoperative IOP to within 2 mmHg of baseline preoperative IOP, 47% of treated eyes compared with 78% of control eyes reached this endpoint by day 32 (Fig 3). This difference in time to IOP failure for treated versus control eyes was statistically significant ($P = 0.03$).

The blebs lasted longer in treated eyes compared with control eyes (Fig 4). Ninety-two percent of the blebs in the control eyes compared with 67% of the blebs in treated eyes had failed by day 32. Although bleb duration was not significantly different in either of the two experimental groups analyzed separately, a statistically significant difference was achieved when the two groups were combined ($P = 0.05$).

Of the five eyes that developed conjunctivitis with discharge, four were in the mitomycin-treated group. Three of these four eyes had received polymers with the higher concentration of mitomycin. Conjunctival injection was transient and not significantly different between control and experimental eyes. Anterior chamber inflammation also was transient but lasted longer in experimental eyes ($P = 0.01$). These reactions gradually cleared over 1 to 3 weeks. Sectoral corneal haze near the sclerostomy site was transient and similarly distributed among control and experimental eyes of rabbits in the group that received the lower dose of mitomycin. However, sectoral corneal haze was present in seven (70%) of the eyes treated with the higher dose of mitomycin compared with three (30%) control eyes. In this latter group, corneal haze was transient in all but two mitomycin-treated eyes. No gross len-

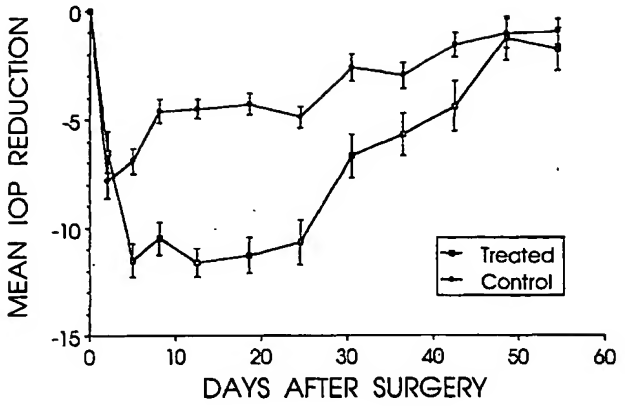

Fig 2. Postoperative IOP reduction from baseline preoperative IOP for treated and control eyes. Open boxes represent mitomycin-treated eyes. The IOPs are significantly lower in the experimental eyes (0.02 mg and 0.06 mg mitomycin) between days 8 and 25.

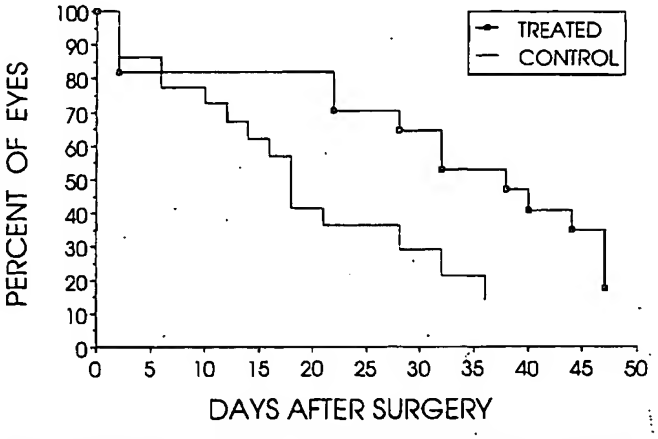

Fig 3. Survival curve of eyes with postoperative IOP within 2 mmHg of baseline preoperative IOP. Experimental eyes (0.02 mg and 0.06 mg mitomycin) lasted longer than control eyes.

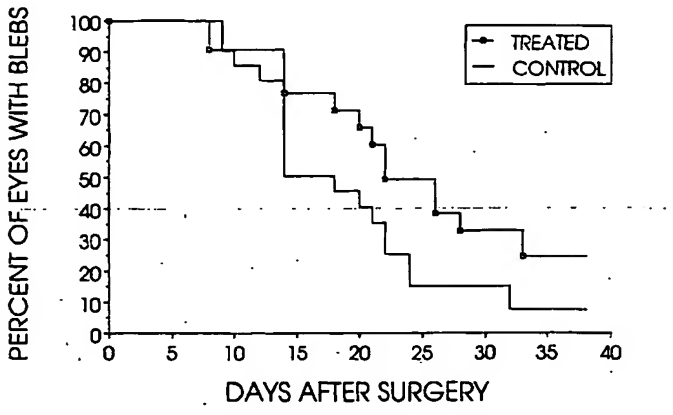

Fig 4. Survival curve of blebs after filtering surgery. Blebs lasted longer in experimental eyes (0.02 mg and 0.06 mg mitomycin).

Table 2. Pathologic Findings at Filtration Site

	Eyes Examined at Two Weeks		Eyes Examined at Eight Weeks	
	Control (n = 3)*	Mitomycin C (n = 3)*	Control (n = 12)*	Mitomycin C (n = 12)*
Peripheral anterior synechiae	2	1	6	6
Iris/ciliary body prolapse into sclerostomy	0	0	2	3
Fibrosis and iris occluding sclerostomy	2	0	2	4
Fibrosis occluding sclerostomy	0	0	7	5
Open filter sites	0	2	0	0
Vitreous to wound	0	1	1	1

* Number of pathologic findings may exceed the number of eyes examined because of multiple findings in a single eye.

ticular damage or opacification was noted in any of the eyes during the study.

Thirty eyes were sectioned for pathologic findings. Six of these eyes originated from rabbits sacrificed 2 weeks after filtration surgery. The characteristics of the eyes sectioned did not differ from those not sectioned with regard to preoperative and postoperative IOP, bleb survival, or ocular toxicity. Of the 24 eyes harvested at study termination, 23 showed closed filtration sites. In one eye, the filtration site could not be identified. Eleven eyes, including seven treated with mitomycin, showed iris adherent to the sclerostomy site. In 5 of these 11, iris and ciliary body prolapsed through an otherwise open sclerostomy site; in the other 6 eyes, a combination of fibrosis and iris prolapse accounted for the closure of the sclerostomy. The remaining 12 eyes with closed filtration sites, including 5 mitomycin-treated eyes, demonstrated fibrosis at the sclerostomy site. Peripheral anterior synechiae near the sclerostomy site were observed in 12 of the 24 eyes. In 10 of these eyes, including 4 treated with mitomycin, synechiae appeared to completely obstruct the pathway from sclerostomy to the anterior chamber. Vitreous was adherent to the sclerostomy sites in two eyes. Five eyes, including three treated with mitomycin, demonstrated focal corneal clouding near the sclerostomy site. One control eye demonstrated a focal peripheral chorioretinal scar distant from the operated site. No other retinal lesions were observed (Table 2).

From the rabbits sacrificed at 2 weeks, 6 eyes were available for pathologic study. The filtration sites were open in two of the three mitomycin-treated eyes. Grossly observed brown pigment in one sclerostomy corresponded to pigment-laden macrophages, fibrin, and blood lining the tract. In the other mitomycin-treated eye, vitreous and fibrous membranes occluded the sclerostomy site, and peripheral anterior synechiae completely blocked communication to the anterior chamber. The filtration sites were closed in the three control eyes. In one of these eyes, the entrance to the anterior chamber was completely closed by peripheral anterior synechiae and fibrous tissue partially covered the sclerostomy site. In the other two control eyes, the sclerostomy sites were occluded by a combination of fibrosis and apposition of iris and ciliary body.

DISCUSSION

Mitomycin has been shown to be a potent inhibitor of human ocular fibroblast proliferation in cell culture.[21] This antifibroblast activity is believed to be the mechanism whereby mitomycin inhibits the regrowth of surgically excised pterygia.[10–12] Since proliferation of fibroblasts is believed to be one of the contributing factors to filtration failure, mitomycin may prove efficacious in promoting filtration surgical success.

A notable reduction in IOP was noted in rabbit eyes that underwent full-thickness filtration surgery. However, the duration of this reduction was significantly longer when mitomycin was used in conjunction with the surgery. Wilson et al[6] found no differences in IOP between treatment and control rabbit eyes when mitomycin solution versus sterile saline was administered topically to rabbit eyes that had not undergone filtration surgery. The additional fact that bleb survival is significantly longer in the mitomycin-treated eyes in this study suggests a mechanism that involves inhibition of sclerostomy obliteration.

Pathologic findings at 2 weeks after filtration surgery demonstrated that when vitreous loss was not a factor, sclerostomy sites were patent in eyes treated with mitomycin. However, in the eyes examined at 6 weeks, the frequent presence of peripheral anterior synechiae and iris/ciliary body prolapse suggests that failure of filtration cannot always be attributed to fibroblast proliferation at the sclerostomy site.

Postoperative complication of conjunctivitis (four mitomycin-treated eyes and one control eye) occurred primarily in eyes treated with mitomycin. This observed association may be significant, but the low number of eyes in question precludes valid statistical analysis. The fact that the majority of the affected eyes received the higher concentration of mitomycin may suggest that with a lower effective dose, this complication could be avoided in most cases. It is unclear whether onset of conjunctivitis indicates a chemical etiology as opposed to postoperative infection. Previous studies of ocular use of mitomycin have reported minimal ocular toxicity,[6,10–12] especially when used at minimum effective dosages.

Although the reduction in the postoperative IOP was longer for both groups of experimental eyes over control eyes, this effect was greater in the eyes treated with the lower dose of mitomycin. In addition, eyes with sectoral corneal edema and conjunctivitis were notably fewer in this experimental group.

The use of mitomycin-C as an adjunctive treatment to full-thickness filtration surgery may be an efficacious way to delay surgical failure. Few serious side effects are observed when it is used at the lower effective dose reported in this study. Furthermore, a delivery system using bioerodible polymers may enhance efficacy and minimize toxicity. The polymer implant allows sustained and controlled drug delivery near the sclerostomy site where it is needed. With all of these potential advantages, the modulation of glaucoma filtration surgery wound healing with mitomycin-C and bioerodible polymers may hold great promise for improving the outcome in eyes of patients with glaucoma who have poor surgical prognoses.

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